GENE REGULATORY NETWORKS WITH DISTRIBUTED DELAY [1]

© A. Ponossov, A. Shindiapin, Yu. Nepomnyashchikh

A method to study asymptotic properties of solutions to systems of differential equations with distributed time-delays and Boolean-type nonlinearities (step functions) is offered. Such systems arise in many applications, but this particular contribution deals with specific examples of such systems coming from gene regulatory networks. A challenge is to analyze stable stationary points which belong to the discontinuity set of the system (thresholds). We will describe an algorithm of localizing stationary points in the presence of delays as well as stability analysis around such points. The basic technical tool consists in replacing step functions by moderately steep sigmoids (called «logoids») and investigating the smooth systems thus obtained. In addition, we make use of the so-called «linear chain trick» which we, however, apply to the system in question in a slightly modified form.

Let us consider a system of delay differential equations with switch-like nonlinearities

$$\begin{aligned} &\dot{x}_i = F_i(Z_1, ..., Z_n) - G_i(Z_1, ..., Z_n)x_i, \\ &Z_i = Z_i(y_i), \\ &y_i(t) = (\Re_i x_i)(t) \quad (t \geqslant 0; i = 1, ..., n), \end{aligned}$$

describing gene regulatory networks with autoregulation.

A s s u m p t i o n 1.1: F_i, G_i are affine functions in each variable, satisfying

$$F_i(Z_1, ..., Z_n) \geqslant 0, G_i(Z_1, ..., Z_n) \geqslant \delta > 0 \text{ for } 0 \leqslant Z \leqslant 1 \text{ and } i = 1, ..., n.$$

A s s u m p t i o n 1.2: For some $\theta_i > 0$

$$Z_i(y_i) = Z_i(y_i, \theta_i) := \begin{cases} 0 & \text{if } \ y_i < \theta_i \\ 0.5 & \text{if } \ y_i = \theta_i \\ 1 & \text{if } \ y_i > \theta_i \end{cases}$$

A s s u m p t i o n 1.3: The integral operator is given by

$$(\Re_i x_i)(t) = c_0^i x_i(t) + \int_{-\infty}^{t} K_i(t-s)x_i(s)ds, \qquad t \geqslant 0,$$

where $K_i(u) = c_1^i K_i^1(u) + c_2^i K_i^2(u)$, $c_\nu^i \geqslant 0$ $(\nu = 0, 1, 2)$, $c_0^i + c_1^i + c_2^i = 1$, and

$$K_i^1(u) = \alpha_i e^{-\alpha_i u}, \ \alpha_i > 0 \ \ (\textit{the weak generic delay kernel}),$$

$$K_i^2(u) = \alpha_i^2 u e^{-\alpha_i u}, \ \alpha_i > 0 \ \ (\textit{the strong generic delay kernel}).$$

Below we assume that a natural number j $(1 \leqslant j \leqslant n)$ is fixed. For the sake of simplicity we assume in what follows that there is no delay in the variables x_r for $r \neq j$.

[1]The work is partially supported by CIGENE — Centre for Integrative Genetics and by NUFU — Norwegian Programme for Development, Research and Education.

We are investigating *singular stationary points*, i. e. points P^0 belonging to a set where exactly one of the variables y_j assumes the value $y_j = \theta_j$. Then, it can be shown that in a sufficiently small neighborhood of such a point the other functions Z_i are identically equal to 0 or 1: $Z_r(y_r) = B_r$ for any $r \neq j$, where B_r is a Boolean variable. Put $B_R = (B_r)_{r\neq j}$ and

$$\bar{J} := \frac{\partial}{\partial Z_j} F_j(Z_j, B_R) - \frac{\partial}{\partial Z_j} G_j(Z_j, B_R)\theta_j$$

and observe that $\bar{J}$ is, in fact, independent of Z_j, as F_j and G_j are affine with respect to Z_j (and the other variables as well).

The following result is a particular case of the existence theorem proved in [1]:

T h e o r e m 1. *Assume that* $\bar{J}$ *is not zero and the system*

$$\begin{array}{l} F_j(Z_j, B_R) - G_j(Z_j, B_R)\theta_j = 0 \\ F_r(Z_j, B_R) - G_r(Z_j, B_R)y_r = 0 \quad (r \neq j) \end{array}$$

with the constraints

$$\begin{array}{l} 0 < Z_j < 1 \\ Z_r(y_r) = B_r \quad (r \neq j) \end{array}$$

has a solution $\bar{Z}_j$, $\bar{y}_r$ $(r \neq j)$. *Then for any delay operator* $\Re_j$, *described above, there exists a singular stationary point* P^0 *for the main system. This point is independent of the choice of the operator* $\Re_j$.

Stability analysis around singular stationary points is more involved. A typical result is formulated below.

T h e o r e m 2. *Assume that* $c_0^j = 0$. *Let also the assumptions of Theorem* 1 *be fulfilled. Then the following statements are valid:*

1. *If* $\bar{J} > 0$, *then* P^0 *is unstable.*
2. *If* $\bar{J} < 0$, $c_1^j = 0$, *then* P^0 *is unstable.*
3. *If* $\bar{J} < 0$, $c_1^j \neq 0$ *and* $G_j(\bar{Z}_j) < \alpha_j (c_1^j)^{-1}(1 - 2c_1^j)$, *then* P^0 *is unstable.*
4. *If* $\bar{J} < 0$, $c_1^j \neq 0$ *and* $G_j(\bar{Z}_j) > \alpha_j (c_1^j)^{-1}(1 - 2c_1^j)$, *then* P^0 *is asymptotically stable spiral point.*

Analysis of higher order delay kernels has been performed with the help of MATHEMATICA.

REFERENCES

1. *Ponossov A.* Gene regulatory networks and delay differential equations // Special issue of Electronic J. Diff. Eq. 2004. V. 12. P. 117–141.

Ponossov Arcady
Norwegian University of Life Sciences
Norway, Ås
e-mail: arkadi@umb.no

Shindiapin Andrei
Eduardo Mondlane University
Maputo, Mozambique
e-mail: andrei.olga@tvcabo.co.mz

Nepomnyashchikh Yuri
Eduardo Mondlane University
Maputo, Mozambique
e-mail: yuvn2@yandex.ru

Поступила в редакцию 5 мая 2007 г.